Rift Valley Fever

Disease Monograph Series – 05

Virus | Phlebovirus | *Bunyaviridae* | Cattle | Sheep | Goats

IDRC | Bartay

This monograph forms part of a series of disease monographs commissioned by the International Development Research Centre over the period Nov 2015 to April 2016 to inform funding priorities for the Livestock Vaccine Innovation Fund (LVIF). The LVIF is a seven-and-a-half year, CA$57 million partnership between the Bill & Melinda Gates Foundation, Global Affairs Canada and Canada's International Development Research Centre. It focuses on those animal diseases posing the greatest risk to poor livestock keepers in Sub-Saharan Africa, South and Southeast Asia, targeting transboundary diseases to achieve lasting regional impact.

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Acronyms

AU	African Union
AU-IBAR	African Union Inter-African Bureau for Animal Resources
BBSRC	Biotechnology and Biological Sciences Research Council
BMGF	Bill and Melinda Gates Foundation
CVO	Chief Veterinary Officer
DALY	Disability-adjusted life year
DIVA	Differentiate infected from vaccinated animals
DVS	Director Veterinary Services
ELISA	Enzyme-linked immunosorbent assay
FAO	Food and Agriculture Organization of the United Nations
IAEA	International Atomic Energy Agency of the United Nations
IM	Intramuscular
NGO	Non-governmental organization
OIE	World Animal Health Organization
PCR	Polymerase chain reaction
RVF	Rift Valley fever
RVFV	Rift Valley fever virus
SHF	Small holder farmer

SMP-AH	Standard Methods and Procedures in Animal Health Program
TPP	Target Product Profile
WHO	World Health Organization of the United Nations

Executive Summary

Etiology and relevance

In Africa and the Arabic Peninsula where it occurs, Rift Valley fever (RVF) is a major animal and public health problem, in both endemic and epidemic forms. It is caused by a mosquito-borne multispecies single stranded RVF virus of the Phlebovirus genus in the Bunyaviridae family. This zoonotic disease, with significant socio-economic impact, is complicated by the fact that major epizootics occur after intervals that can last several years, thus finding the countries completely unprepared.

The disease has a considerable impact on producers including smallholder farmers, traders, the livestock industry and public health. The costs of an outbreak can be considerable, for example the cost of the East African outbreak in 1997-1998 was estimated at over USD 250 million, and the 2006-2007 outbreak in Somalia was estimated at USD 471 million. RVF has also been taken considerable relevance as a potential bioterrorist threat.

Epidemiology and transmission

In endemic regions, the virus is believed to circulate transovarially in mosquito vectors for years, causing often unnoticed infections and mild disease, until such time that favourable conditions are present to trigger major epidemics. Outbreaks of the disease are associated to the simultaneous presence and circulation of the RVF virus by mosquito vectors, the mosquito pressure (number of breeding sites and hatching frequency), which is highly dependent on environmental conditions, particularly heavy rainfall events; and the distribution of domestic animal hosts, essentially ruminants (goats, sheep and cattle) vulnerable to the increased vector/host contacts at night.

Mosquitoes constitute the major source of transmission of the virus, although in utero transmission to the foetus by the dam in ruminants, camels and other susceptible species can occur. The virus may also infect other animals exposed to abortion or birth products, which contain large amounts of virus, although the importance of this route is still controversial. At present, the major mosquito hosts appear to be members of the genera *Aedes, Culex* and *Anopheles*. Other biting insects might also be able to transmit this virus from viremic animals, although their role (if any) in nature is still uncertain.

In endemic regions, spontaneous abortions among livestock, especially small ruminants, and high mortality rates in new born animals are a hallmark for epidemics of RVF. Between epidemics, this virus can circulate without apparent clinical signs in susceptible species, or there may be sporadic abortions that could be confused with other diseases.

Diagnostics

Suspicion of RVF could generally be made when heavy rains are followed by the occurrence of abortions in sheep, cattle and goats together with fatal disease, particularly in young and pregnant animals. Frequently there is also influenza-like illness in livestock owners. Specimens to be submitted for laboratory confirmation of the diagnosis include heparinized or clotted blood, plasma or serum of live affected animals or tissue samples, including liver, spleen, kidney, lymph nodes and heart blood of dead animals. Samples from aborted foetuses should also be sent. RVF virus can be isolated from blood and the different tissues above.

Control

Given the long and inconsistent inter-epidemic period and the potential devastating nature of outbreaks, it is always recommended that endemic countries institute active and passive surveillance programs, consisting of different actions. The purpose of the active surveillance is to demonstrate the presence or absence of RVFV antibodies (IgM and IgG) and clinical disease in high risk areas with history of the disease. This is generally done through the use of sentinel animals regularly serologically tested, and possibly conducting syndromic surveillance focusing on clinical signs.

For the control of RVF, there is no effective chemotherapy or treatment. Mosquito control although may assist in improving the disease situation during outbreaks, is not often effective as a major control tool. Immunisation has been so far the most effective control strategy.

Vaccination and vaccination strategies

To date there are three commercially available vaccines: the inactivated RVF vaccine, produced in South Africa and in Egypt, the live attenuated vaccine based on the Smithburn virus strain produced in South Africa and in Kenya, and the more recently registered RVF Clone 13, produced in South Africa.

While the live attenuated RVF Smithburn vaccine has been the most widely used vaccine for many years, it has safety shortfalls, including risk of triggering abortion in a small proportion of vaccinated pregnant animals; thus is not recommended for use in pregnant animals. The inactivated RVF vaccine, which would have been suitable for use even in the middle of an outbreak, requires booster doses, making it impractical for use in most vaccination programs in Africa. The RVF Clone 13 was successfully used in the 2008 RVF outbreak in South Africa. But due to stability problems with the vaccine, the production of the vaccine has been discontinued.

The cyclical nature of RVF epidemics and the subsequent long inter-epidemic periods have resulted in many countries considering the use of vaccination only when there is the first indication of an outbreak, with negative consequences, as the pressure increases on the limited manufacturers to suddenly supply enough vaccines to all requesting countries. Alternatively, control strategies that promote the establishment of solid herd immunity in

the livestock population in endemic regions are more likely to reduce the devastating impact of severe outbreaks. Yearly vaccination, practiced in limited number of countries, such as South Africa, would contribute to increased herd immunity. Two strategies have been considered for addressing the issue of vaccine availability and improved herd immunity: (1) the RVF vaccine bank (or strategic stock) and (2) use of combination vaccines including RVF which would then rely on the regular vaccination of animals for the second, more commonly used vaccine, such as Lumpyskin disease in cattle and sheep and goat pox in sheep and goat, in order to build immunity in vaccinated animals to RVF.

The future of RVF vaccines and vaccination

Several research groups around the world have been working on developing new candidate vaccines using different strategies. While almost no improvement to the inactivated vaccine approach has been reported, despite extensive progress globally on adjuvant technology, RVF vaccine research has seen almost all novel technologies been applied to it: reverse genetic to generate deleted viruses, virus like particle, virus-vectored vaccines, subunit vaccines, plant expression, combination vaccines etc. Sadly none of these new generation vaccines have been developed industrially nor commercialised.

One of the reasons that have prevented the evaluation of these candidate vaccines in target animal is the limited availability of validated challenge models. The zoonotic nature of RVF and the lack of available human vaccine have also made it impossible for many research groups in free or endemic countries to conduct target animal efficacy or safety studies requiring challenge with virulent viruses.

A number of key characteristics for the ideal vaccine and target product profile are not necessarily included in existing or candidate vaccines developed to date. For new candidates, some of the characteristics such as DIVA, safety in all categories, prevention of viremia etc., have not been confirmed due to lack of target animal data. The DIVA aspect, not possible in any of the currently commercial vaccines, has not been confirmed on any known candidate vaccine due to among other reasons the inability to develop specific serological tests (ELISA) based on most of the RVF proteins not present in the candidate vaccine. Subsequent to the above points, the way forward with RVF vaccine and vaccination would be an assessment of already developed vaccine candidates for their suitability in meeting the key requirements, and on how they could be included in effective vaccination strategies.

A number of critical points are needed to be considered in order to achieve this, and include:

1. Need to validate an effective challenge model and validate in vitro correlates to protection
2. Need to assess candidate vaccines that meet theoretically most of the key characteristics of the idea vaccine through further target animal studies. The selection of such candidates should also take into account the ability for their easy production at industrial scale

3. For candidate vaccines with a DIVA potential, need to develop and validate their companion diagnostic test
4. Where possible need to develop or include RVF into multivalent vaccines, in order to increase RVF vaccine uptake
5. Need to develop the most suitable vaccination strategies

The implementation of appropriate vaccination strategies, or control strategies involving RVF vaccines will be the best way to improve RVF prevention and control, given the fact that most endemic countries do not vaccinate during inter-epidemic periods or around declared epidemics. The strategies should include regional approaches relying on tools such as vaccine banks, multi-vaccines, field tools for active surveillance (sentinel animals and field diagnostic assays etc.). Pilot programs for the development and consolidation of adapted vaccination strategies could be conducted at regional level in Africa (Southern African community region, SADC or East African Community, EAC), building on lessons learned to date from partial joint programs.

Clinical disease overview

Etiology

Rift Valley Fever (RVF) is a mosquito-borne multispecies zoonotic disease affecting livestock and other species, caused by the RVF virus.

Following the first description of a disease resembling Rift Valley fever (RVF) and affecting sheep by Montgommery in Kenya in 1912-13, Rift Valley fever was formerly identified in 1930 during a major outbreak in a farm near Lake Naivasha in Kenya [10]. The virus responsible for this outbreak was isolated from blood and liver of infected sheep and called Rift Valley fever virus (RVFV).

A worthwhile noting element for the RVF virus is the fact that the NSs is an important virulence factor. While RVFV replicates in the cytoplasm, NSs is the only viral protein present in the nucleus of the host cell where it forms filamentous structures [47][56] interacting with several cellular proteins and causing various effects responsible for RVFV pathogenicity.

Although different lineages have been described for RVF virus, resulting in different manifestation of the disease, there is only one serotype of RVFV, hence any RVF vaccine protects against all lineages.

Virus structure

RVF virus belongs to the Phlebovirus genus of the Bunyaviridae family. The RVF virus is enveloped and spherical with a diameter of 80-120 nm. Like all the members of the family, it possesses a single-stranded tripartite RNA genome composed of 3 segments: the large (L), the medium (M), and the small (S) segments, as illustrated below and in Figures 2. The L segment encodes for the L protein, the M segment is the precursor to the glycoproteins GN and GC and the two non-structural proteins 78 KDa and 14 KDa; and the S segment codes for the N nucleoprotein and the non-structural NSs protein using an ambisense strategy [16]. The L and M segment are of negative sense polarity.

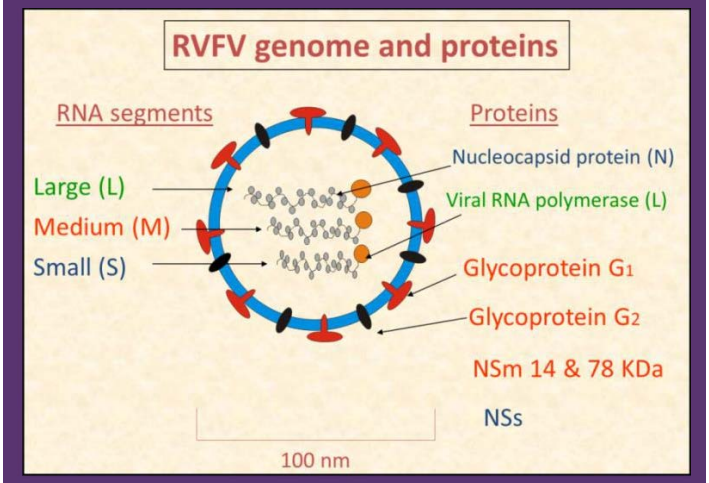

Figure 1: Rift Valley Fever virus structure

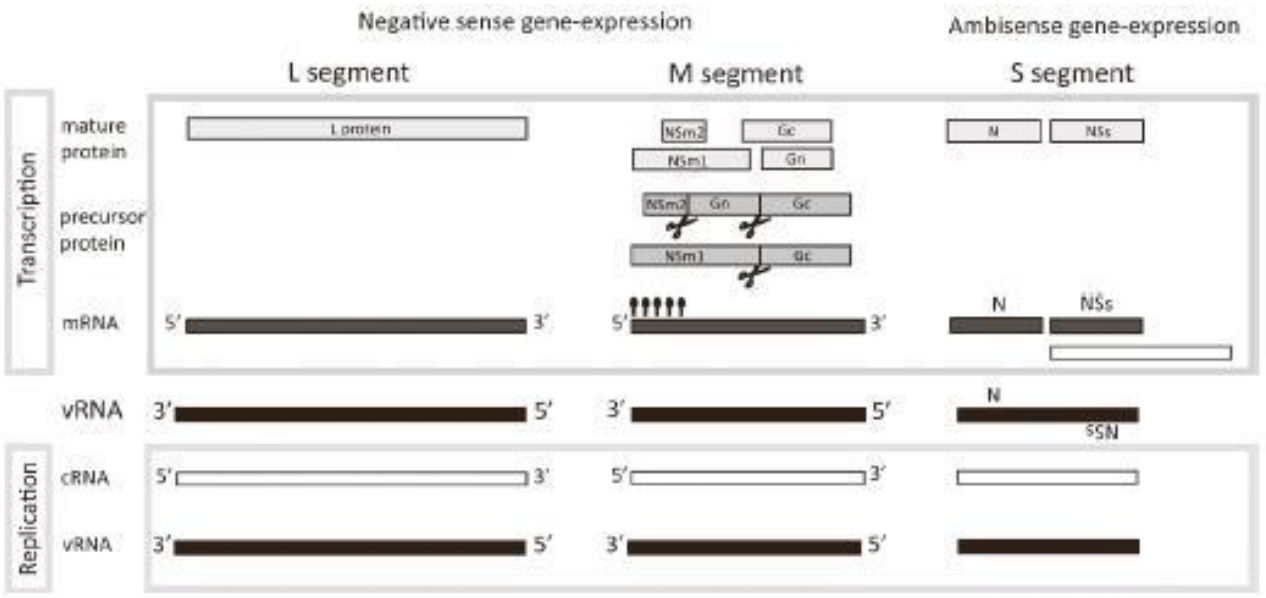

Figure 2: Rift Valley Fever virus genome segments and replication strategies. Precursor proteins expressed from the first and second AUG on the M segment are shown [29]

Epidemiology

Susceptible animal species

A large number of mammalians are susceptible to RVF, while birds, reptiles and amphibians are refractory. Susceptibility varies between species and also with age of animals as illustrated in Table 1 below. Humans are susceptible to the disease, which manifests itself in a small percentage as a fatal viral haemorrhagic fever.

Distribution

To date RVF has only been reoprted on the African continent and the Arabian peninsula. Following the first reported outbreak of RVF in Kenya in 1930, the virus remained endemic in the region and caused sporadic outbreaks, especially after periods of exceptionally heavy rains. Beside those countries linked to the Great Rift Valley formation, which stretch from the Red Sea through East Africa to Madagascar, serious outbreaks of RVF have occurred in Egypt, Mauritania and Senegal.

The first human fatalities directly attributable to RVFV infection were reported in South Africa in 1975 [33][52]. Abortion of sheep is observed almost systematically during the RVF outbreaks. In Madagascar, RVFV was

reported as early as 1978 and in 1990-91 but after a silence of 20 years, the most important emergence occurred in 2010.

Table 1: Species susceptibility to RVF (Adapted from [37])

Extremely susceptible (70-100% mortality)	Highly susceptible (20-70% mortality)	Moderately susceptible (less than 10% mortality)	Resistant (inapparent infection)	Refractory (not susceptible)
Lambs	Sheep	Cattle	Camels	Birds
Kids	Calves	Goats	Equids	Reptiles
Puppies		African buffalo	Pigs	Amphibians
Kittens		Asian buffalo	Dogs	
Mice		S. American monkeys	Cats	
Hamsters		Asian monkeys	African monkeys	
Certain other rodents		Certain rodents	Baboons	
		Humans	Rabbits	
			Guinea pigs	
			Certain other rodents	

Importantly, the virus extended its territory in 2000 causing a major outbreak in Saudi Arabia and Yemen. Several other African countries have reported small outbreaks or virus circulation monitored by the presence of RVF specific antibodies and in some cases virus isolation. In 2008, the circulation of the virus was reported for the first time in the Comoros Islands. Figure 3 shows a map with the countries with endemic RVF, and countries at risk. For additional information see Secion 3.

RVF Transmission

More than 30 species of mosquitoes are potentially involved in RVFV transmission, the main vectors belonging to the *Aedes, Culex* and *Anopheles* genera [30][50][45]. It is important to note that the virus has been isolated from several insects, including ticks and culicoides. However until now, there is no evidence of the virus ability to replicate in these species as laboratory experiments suggest that some of these species are not competent vectors for transmission. Potential mechanical and/or biological vectors include stable flies (*Stomoxys spp*.), tsetse flies (*Glossina morsitans*), sandflies (*Lutzomyia longipalpis*), biting midges (*Culicoides variipennis*),

blackflies and ticks. Table 2 shows the different species incriminated in the transmission of RVFV during the outbreaks in East Africa and the Middle East

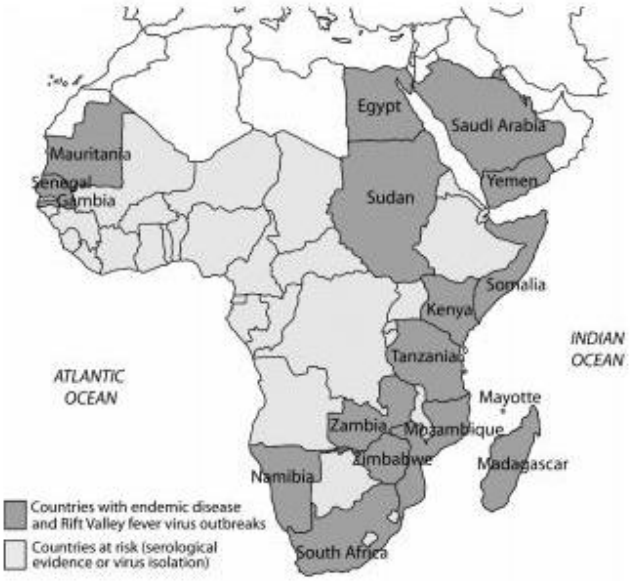

Figure 3: Map showing RVF endemic countries, and countries at risk. (Source: [29])

Table 2: Mosquito species incriminated in the transmission of RVFV during the outbreaks recorded in East Africa and the Middle East (Source: [19])

Year of outbreak	Affected country	Collected mosquitoes
1997–1998 and 2006	Kenya	*Culex zombaensis, Culex poicilipes, Culex bitaeniorhynchus, Culex quinquefasciatus, Culex univittatus, Anopheles coustani, Anopheles squamosus, Aedes mcintoshi, Aedes ochraceus, Aedes pembaensis Mansonia africana, M. uniformis*
1997–1998 and 2007	Tanzania	*Aedes mcintoshi*
1997–1998	Eastern Africa	*Culex theileri*
1977	Egypt	*Culex pipiens*
2000	Kingdom Saudi Arabia	*Culex pipiens, Aedes vexans arabiensis, Ae. Vittatus, Ae. (Stegomyia) nilineatus, Aedes vexans arabiensis,* and *Culex triteniorynchus*
2000	Yemen	Not defined
2007–2008	Sudan	*Cx pipiens, Cx. Poicilipes, An. arabiensis, An. coustani, Ae. aegypti*
1997–1998 and 2006–2007		Not defined

RVF virus can be transmitted *in utero* to the foetus of ruminants, camels and other species. This virus may also infect other animals exposed to abortion or birth products, which contain large amounts of virus; however, the importance of this route is controversial.

Virus shedding in secretions and excretions from infected ruminants is not important in spreading Rift Valley fever.

Humans can acquire RVF virus by direct contact with infected tissues, contact with aerosolized viruses generated in laboratories or during slaughter, or from mosquitoes. The relative importance of mosquito-borne exposure and exposure to infected animal tissues continues to be debated. Drinking raw (unpasteurized) milk is a significant risk factor for human infection, although definitive proof for this route is lacking. Vertical transmission to human infants has been demonstrated in at least 2 cases. Person-to-person (horizontal) transmission does not seem to occur, but the blood and tissues of patients might be sources of exposure for medical personnel.

Epidemic RVF disease patterns

A number of factors play a role in the occurrence of outbreaks:

(i) the presence and circulation of the RVF virus by mosquito vectors;

(ii) the mosquito pressure (number of breeding sites and hatching frequency), which is highly dependent on environmental conditions, particularly rainfall events; and

(iii) the distribution of domestic animal hosts, essentially ruminants (goats, sheep and cattle), vulnerable to increased vector/host contacts at night. However, there is extensive species susceptibility to RVF, as set out in Table 1.

In endemic countries, RVF tends to reoccur at varying interval periods that can last several years. The patterns of outbreak in certain countries, such as Kenya, have been studied and used to develop risk maps, which are useful for control strategies. (Figure. 5; [37])

Ideal conditions for emergence of RVFV-infected mosquitoes occur after flooding when unusually heavy rains affect the country. The *Aedes spp*. floodwater mosquito is the primary vector: it transmits the virus trans-ovarially and when surface water accumulates the infected mosquito eggs which were dormant, can hatch and give birth to infected mosquitoes which feed on livestock or humans and transmit the virus. Infected ruminants develop a high viremia providing a source for secondary vectors such as *Culex* spp. mosquitoes to be infected and further spread the virus by biting other animals and humans. During epidemics (Figure 4), the virus can also be transmitted directly from infected to healthy ruminants. Transmission to humans through contact of infected animal tissues and blood appears to be a common mean of infection [15]. This is attested by the number of human cases among butchers, veterinarians and shepherds who contaminate themselves via abrasions of the

skin, or through mucosal membranes of the respiratory tract. For this reason, it is highly recommended to veterinarians to wear gloves, gowns and face masks. As stated earlier, the suggestion that humans can become infected after consumption of raw milk needs still to be confirmed [1][35].

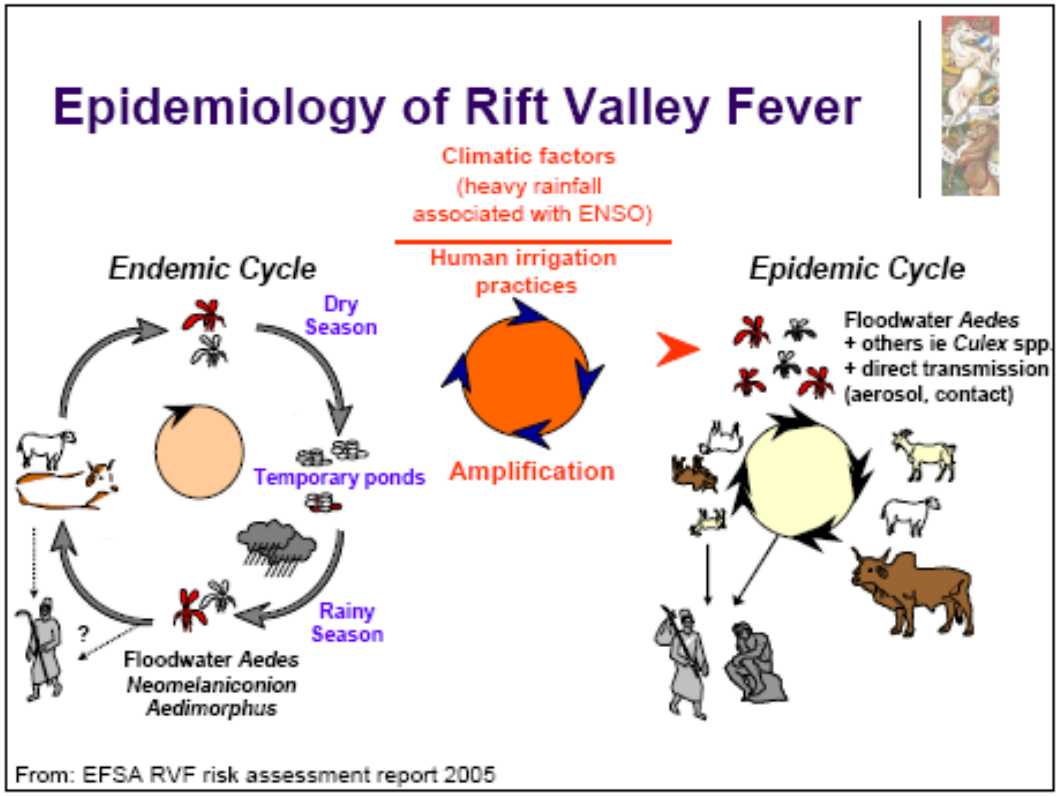

Figure 4: Epidemiology of RVF: Endemic and epidemic cycles. Source: EFSA RVF risk assessment report, 2005

The mechanisms that maintain RVF virus in nature and cause it to emerge in epidemic form are incompletely understood, and might differ between areas. It is believed that there is a transovarial transmission in mosquitoes: mosquito eggs remain dormant in soil for long periods of time, surviving long dry spells. There may be low level circulation of the virus. These eggs would hatch in big numbers during heavy rainfall.

Transmission cycles are best understood in savannah regions, where the virus is thought to survive between outbreaks in the dried eggs of Aedes mosquitoes found in shallow depressions in the soil (dambos). Infected mosquitoes are thought to hatch when the dambos fill after heavy rainfall, and initiate transmission cycles involving additional mosquito species, and animals that act as amplifying hosts. The vertebrate amplifying hosts are thought to be critical in propagating epidemics. Virus transmission has also been demonstrated at low levels in livestock, wildlife and humans during interepidemic periods. Infection cycles in some other climates, such as forested regions, are poorly understood and might differ from this pattern.

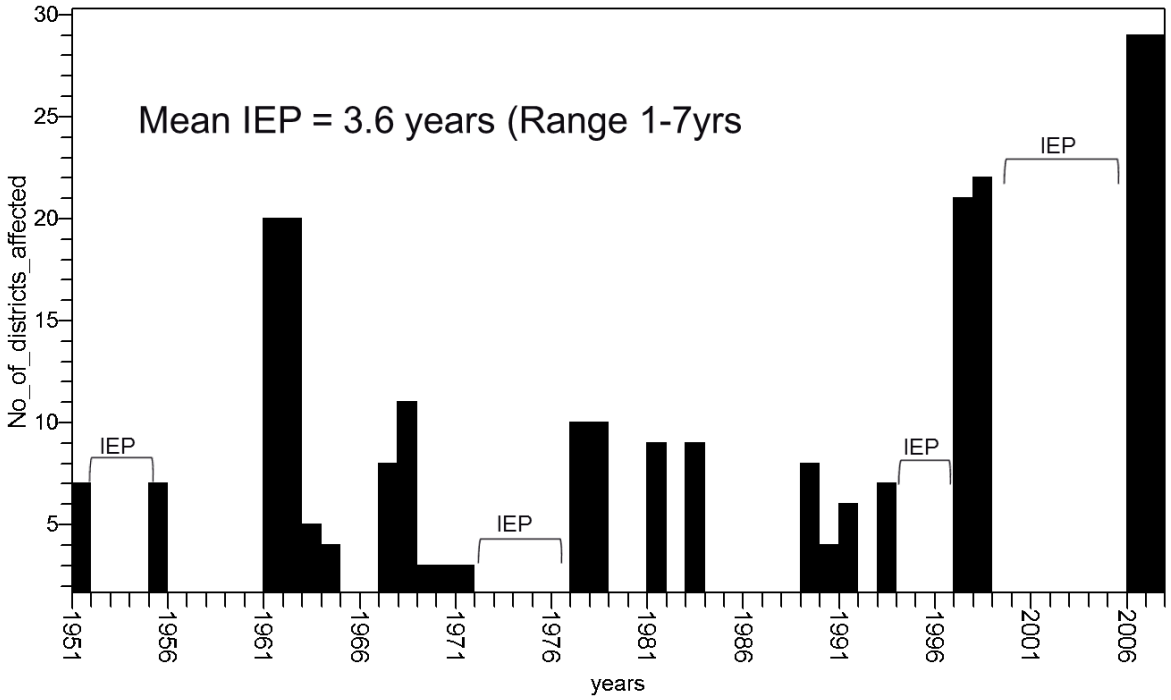

Figure 5: Number of districts affected over time in Kenya, showing the Interval between epidemic cycles [37]

Clinical Signs

Table 3 below summarises the major clinical signs observed in ruminant livestock.

In endemic regions, epidemics of RVF are characterized by high mortality rates in new born animals and abortions in adults. Between epidemics, this virus can circulate without apparent clinical signs in susceptible species, or there may be sporadic abortions that could be confused with other diseases.

Clinical signs depend on the species of animal affected and conditions such as age and pregnancy. During epidemics the occurrence of numerous abortions and mortalities among young animals, together with disease in humans, is characteristic. Pregnant sheep and cattle affected by this disease will almost always abort (80-100%). Young lambs and calves develop a fever, become weak and die very suddenly. The mortality rate in young animals is very high whereas mortality in adult sheep is about 20 per cent and about 10 per cent in adult cattle. Adult sheep and cattle may have nasal discharge, excess salivation, and loss of appetite, weakness, or diarrhoea.

In lambs where RVF is usually most severe, nonspecific signs of fever, anorexia, weakness and lymphadenopathy are common. Haemorrhagic or fetid diarrhoea, melena, regurgitation, signs of abdominal pain, a serosanguineous or bloodstained mucopurulent nasal discharge and elevated respiratory rate may also be seen. Very young lambs and kids with clinical signs rarely survive longer than a few days, and often die with 24 hours.

Older animals may die acutely or peracutely, recover from the illness, or become infected with few or no clinical signs. Similar signs have been reported in young calves, although some sources have reported that icterus is more likely, and survival rates appear to be higher.

Abortions, apparently unrelated to the gestation period, are the most characteristic signs in adult sheep, goats and cattle. There are also reports of abortions in wild ruminants including African buffalo, a waterbuck (*Kobus ellipsiprymnus*), a springbuck (most likely *Antidorcas marsupialis*) and a blesbuck (probably *Damaliscus dorcas*). Some pregnant animals have few or no clinical signs other than abortion, while others become ill or die.

Table 3: Summary of the RVFV clinical signs in livestock

Cattle	Sheep
Calves (highly susceptible)	Newborn labs or under 2 weeks of age (extremely susceptible)
• Fever (40-41°C) • Inappetence • Weakness and depression • Bloody or fetid diarrhoea • More icterus than in lambs	• Biphasic fever (40-42°C); subsides just prior to death • Anorexia, in part due to disinclination to move • Weakness, listless • Abdominal pain • Rapid, abdominal respiration prior to death • Death within 24-36 hours
Adults (moderately susceptible)	Lambs over 2 weeks of age (highly susceptible) and adult sheep (SAME FOR GOAT)

• Often inapparent infection but some acute disease • Fever lasting 24-96 hours • Dry and/or dull coat • Lachrymation, nasal discharge and excessive salivation • Anorexia • Weakness • Bloody/fetid diarrhoea • Fall in milk yield • Abortion rate may reach 85% in the heard	• Peracute disease: sudden death with no appreciable signs. • Acute disease more often in adult sheep. • Fever (40-42°C) lasting 24-96 hours • Anorexia • Weakness, listlessness and depression • Increased respiratory rate • Vomiting • Bloody/fetid diarrhoea • Mucopurulent nasal discharge • Icterus may be evident in a few animals • In pregnant ewes, “abortion storms”

Diagnosis

Suspicion of RVF could generally be made when heavy rains are followed by the occurrence of abortions in sheep, cattle and goats together with fatal disease, particularly in young and pregnant animals, which is marked by necrotic hepatitis and widespread haemorrhages. Frequently there is also influenza-like illness in farm workers.

Specimens to be submitted for laboratory confirmation of the diagnosis include heparinized or clotted blood, plasma or serum of live affected animals or tissue samples, including liver, spleen, kidney, lymph nodes and heart blood of dead animals. Samples from aborted foetuses should include brain since this is usually less autolysed or putrefied than viscera.

The OIE recognized tests are as follows:

- Identification of the agent:
    - Isolation in cell culture
    - Isolation in suckling mice
    - Reverse transcription PCR (agarose based and real time)
    - Antigen detection by antigen ELISA
    - Histopathology
- Serology:

- IgM ELISA: (for recent infection)
- Indirect IgG ELISA
- Virus neutralisation (the prescribed test for international trade)

Table 4 shows the tests recommended by the OIE for the different purposes: to demonstrate population or individual freedom, confirmation of clinical cases, etc.

Table 4: Tests recommended by the OIE [57]

	Purpose					
Method	Population freedom from infection (non-vaccinated animals)	Individual animal freedom from infection prior to movement	Contribute to eradication policies	Confirmation of clinical cases (2)	Prevale ce of infection-surveillance	Immune sattus in individual animals or populations post-vaccination
Agent identifictaion (3)						
Virus isolation in cell culture	-	-	-	+++	+	-
Virus isolation in suckling mice	-	-	-	+	+	-
RT-PCR	-	-	-	+++	+	-
Antigen detection	-	-	-	++	+	-
Histopathology with immuno-histochemistry	-	-	-	++	-	-
Detection of Immune response (4)						
ELISA	+++	++	+++	++	+++	+++
Virus Neutralisation	+++	+++	+++	++	++	+++

Key: +++ = recommended method; ++ = suitable method; + = may be used in some situations, but cost, reliability, or other factors severely limits its application; - = not appropriate for this purpose.
Although not all of the tests listed as category +++ or ++ have undergone formal validation, their routine nature and the fact that they have been used widely without dubious results, makes them acceptable.
RT-PCR = reverse-transcription polymerase chain reaction; ELISA = enzyme-linked; immunosorbent assay; VN = Virus neutralisation.

Indirect IgG ELISA's are the tests most commonly used in low & middle income countries, even though in limited manner. The commercially available tests are generally expensive therefore limiting their use in most control programs

IgG RVF ELISA include whole virus antigen and those based on the nucleoprotein

Due to the lack of DIVA vaccine to date, there is no DIVA diagnostic assay available, although the current ELISA tests based on expressed proteins could be considered where appropriate

Zoonotic disease

Humans can acquire RVF virus by direct contact with infected tissues, contact with aerosolized viruses generated in laboratories or during slaughter, or from mosquitoes. The relative importance of mosquito-borne exposure and exposure to infected animal tissues continues to be debated. Drinking raw (unpasteurized) milk is a significant risk factor for human infection, although definitive proof for this route is lacking. Vertical transmission to human infants has been demonstrated in at least 2 cases. Person-to-person (horizontal) transmission does not seem to occur, but the blood and tissues of patients might be sources of exposure for medical personnel.

In humans, people with RVF will either show no symptoms or develop a mild illness. Signs of illness include fever, weakness, myalgia (muscle pain), back ache, dizziness, liver abnormalities, and weight loss. In some patients, the illness can progress to haemorrhagic fever, encephalitis (inflammation of the brain), or ocular disease (inflammation of the eye, blindness). Severe complications develop in 1-4% of cases though most people recover within four to seven days. Approximately one per cent (1%) of humans infected with Rift Valley fever dies of the disease.

Incidence and Prevalence in Selected Countries

Global

RVF has up to now been restricted to the African continent and the Middle East, both in enzootic and epizootic (and epidemic) ways, with the epizootic and epidemic forms being generally what is widely publicised and reported. Figure 6 and Table 5 show the countries where the disease is endemic and those where epizootics have been reported. In the last decade RVF has been reported in Somalia (2006–2007), Kenya (2006–2007), Tanzania (2007), Sudan (2007–2008), Comoros (2008), Madagascar (2008–2009), South Africa (2008, 2009, and 2010), Mauritania (2010), Botswana (2010), and Namibia (2010).

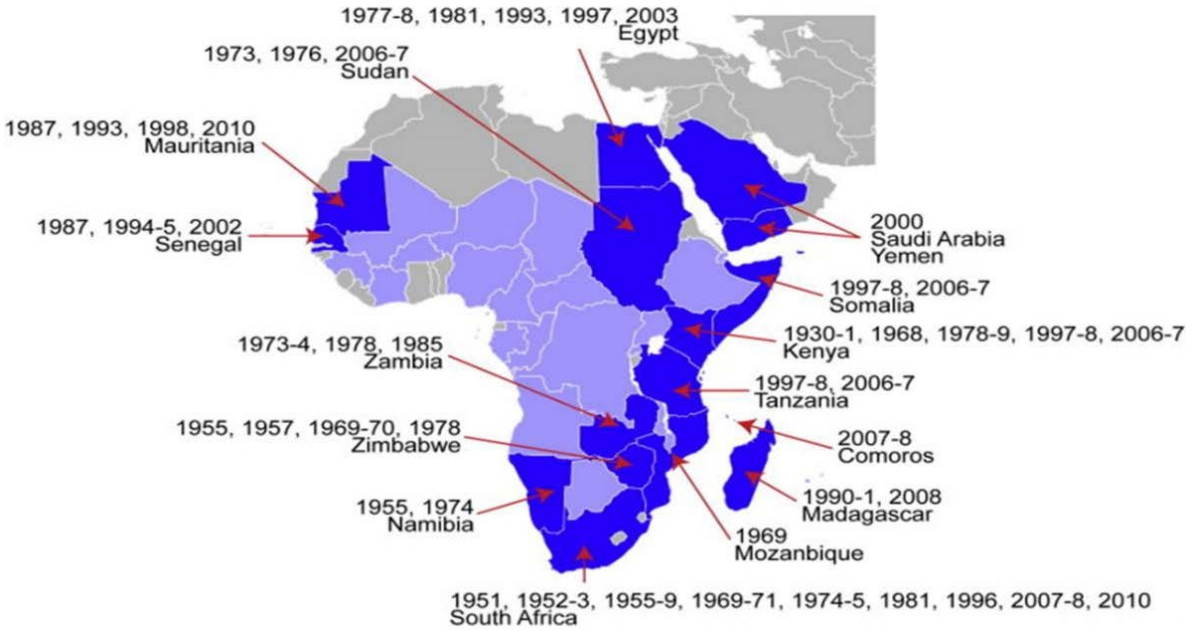

Figure 6: Distribution of RVF as of 2011. Countries that have experienced substantial epizootics and epidemics are shown in dark blue, while those with serological evidence or virus isolation are marked with light blue. (Source: [51])

Table 5: Ten leading disease losses globally by livestock disease units (LSU) loss

Year	Place	Reported deaths in
1930	Kenya	sheep
1950-51	Kenya	sheep
1975	South Africa	sheep cattle, humans
1977	Egypt	humans
1987	Mauritania, Senegal	humans, sheep
1991,96-97	Egypt	humans, sheep
1997-98	Kenya, Somalia, Tanzania	humans, sheep
1998-99	Mauritania, Senegal	humans, sheep
2000-2001	Saudi Arabia, Yemen	humans, sheep
2007-2008	Sudan	humans, sheep
2008-10	South Africa	humans, sheep, cattle
2010	Mauritania	humans, sheep, cattle
2010	South Africa	humans, sheep
2010	Madagascar	humans, sheep

Regional

Incidence data by country

The number of outbreaks reported can be obtained from the OIE and from AU-IBAR. The information is not always similar, as many countries do not seem to report, or to do it in a routinely manner.

1- OIE: The number of outbreaks reported to the OIE in the countries of interest, can be seen in Table 6 below. Note that the disease is not present in the Asian countries of interest.

Table 6: Number of RVF outbreaks reported to the OIE between 2005-2015 (Numbers given only for the target countries) Source: OIE.
http://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/statusdetail.

Country	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
West Africa											
Burkina Faso	-	-	-	-	-	-	-	-	-	-	-
Ivory Coast	-	-	-	-	-	-	-	-	-	-	-
Mali	0	0	0	0	0	0	0	0	0	0	-
Senegal	0	0	0	0	0	0	0	+?	4	1	1
East Africa											
Ethiopia	0	+	0	0	0	0	0	0	0	0	-
Kenya	0	21	15	0	0	0	0	0	0	0	0
Rwanda	-	0	0	0	0	0	0	4	26	-	-
Tanzania	0	?	19	0	0	0	+?	0	0	0	0
Uganda	0	0	0	0	0	0	0	0	0	0	-
Southern Africa											
Madagascar	+?	+?	+?	18	1+	0	0	0	0	0	-
Malawi	+?	+?	+?	+?	+?	+?	+?	+?	?	-	-

Mozambique	0	0	4	+?	0	0	0	0	6	4	-
South Africa	0	0	0	31	40	492	134	0	0	0	-
Zambia	-	0	0	0	0	0	0	0	0	0	-

2- AU-IBAR: The number of outbreaks reported to AU-IBAR is included in the Pan African Animal Resources Year Book. (**http://www.au-ibar.org/pan-african-animal-resources-yearbook?showall=&limitstart**=) and can be seen for the countries of interest in Table 7 below.

Table 7: Number of RVF outbreaks reported to the AU-IBAR from 2005 to 2015 (numbers given only for the target countries). Source: AU-IBAR Year Books.

Country	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
West Africa											
Burkina Faso	-	-	-	-	-	-	-	-	-	-	
Ivory Coast	-	-	-	-	-	-	-	-	-	-	
Mali	-	-	-	-	-	-	-	-	-	-	
Senegal	-	-	-	-	-	-	-	-	10	1	
East Africa											
Ethiopia	-	-	-	-	-	-	-	-	-	-	
Kenya	-	-	+	-	-	-	-	1	1	2	
Rwanda	-	-	-	-	-	-	-	-	-	-	
Tanzania	-	-	+	-	-	-	-	-	-	-	
Uganda	-	-	-	-	-	-	-	-	-	-	
Southern Africa											
Madagascar	-	-	-	1	-	-	-	-	-	-	

Malawi	-	-	-	-	-	-	-	-	-	-	
Mozambique	-	-	-	-	-	-	-	-	-	-	
South Africa	-	-	-	34	41	330	74	-	-	-	
Zambia	-	-	-	-	-	-	-	-	-	-	

There is a very good and recent systematic review of the Rift Valley fever epidemiology from 1931-2014 by Nanyingi et al. [38]. In this publication, the gradual spread and geographical extend of the disease is presented. See Figure 7 below.

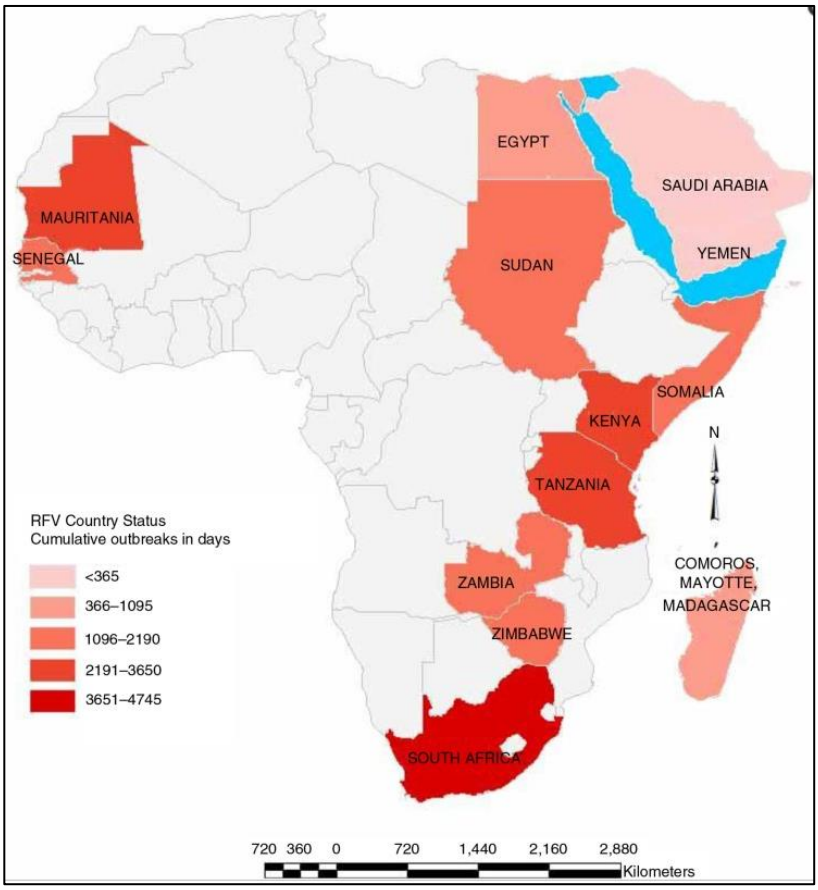

Figure 7: Map of Africa and the Arabian Peninsula illustrating the spatial and temporal distribution of Rift Valley fever cumulative outbreaks in days from 1997-2012. Source: [38])

Incidence data by country

The information below has been obtained from PubMed and internet engine search. The information by country is limited, as it tends to focus on the outbreaks, and not in the inter-epidemic periods.

Table 8: Prevalence of RVF in the different countries (Data from 2000-2015)

Country	Year	Area	Species	N samples tested	% Positive	Reference(s)
Burkina Faso	2014	Northern and Central	Cattle, sheep and goats	520	Seno and Sonum: 7.67 Yatenga: 20 Oubritenga: 22.5	4
	2013	Northern	Camels	270	SNT: 51.85	5
Côte d'Ivoire						No recent publications
Ethiopia						No recent publications
Kenya	2015	Northeast	Humans	1082	15	26
	2007	From AIDS indicator survey	Humans	1091	4.5	42
Madagascar	2009	Highlands	Cattle	2009: 894 2010: Anorana 7 Antanif: 39	2009: 28 2010: Anorana: 14 Antanifotsy: 26	40
	2008	Country survey	Ruminants	Cattle: 3437 Sheep: 227 Goats: 762	Recent infections: Cattle: 0.3 Small ruminants: 3.3 Past infections: Cattle: 25.8	22

					Small ruminants: 24.7	
Malawi						No publications found
Mali					Serological	No recent publications.
Mozambique	2010-2011	Maputo province	Cattle	404	36.9	29
Rwanda						No publications found
Senegal	2012	Case contacts of a patient in Ibel and Thiokoye	Humans	115 contacts with patient + 218 patients with febrile disease	Only 3 tested positive. Assumed infected for being in contact with animals coming from Mauritania	46
	2007	211 locations		16738		9
	2004	Ferlo region	Small ruminants	260	2.6	8
South Africa	2014	Kruger National Park and Hluhluwe-iMfolozi Park	Buffaloes	Kruger: 138 Hluhluwe: 110	6.1	14
	2008-2012	Kruger National Park	Buffaloes	227	Crocodile Bridge: 36.3 Lower Sabie: 10.3	3
	1996-2007	Kruger National Park	Buffaloes	1615 (82 herds)	Herd prevalence per year: 2007: 5 2006: 3 2005: 9 1999: 10	3

					1998: 18 1996:5	
Tanzania	2013	Eastern and Western Rift Valley ecosystems	Ruminants	1435 Sheep: 148 Cattle: 756 Goats: 531	25.8 Sheep: 29.7 Cattle: 27.7 Goats: 22	44
	2012	Kilombero and Ulanga	Humans	Kilombero: 327 Ulanga: 279	Kilombero: 11.6 Ulanga: 11.8	48
	2011?	Kigoma region	Small ruminants	411	Kigoma: 12 Kibondo: 2.3 Kasulu: 0.8 Sheep: 12.5 Goats: 4.7	23
	2010	Northern Tanzania	Camels	109	Individual: 27.5 Herd level: 78.5	49
	2007-2008	Mbeya	Humans	1228	Overall: 5.2 Close to lake Malawi: 29.3 (N:150)	18
Uganda						No recent publications
Zambia						No recent publications

Economic and Social Impacts at Global and Regional Levels, and in Selected Countries

Enzootic and epizootic RVF have generally significant socio-economic impact in affected areas, essentially due to the zoonotic nature of the disease and morbidity and mortality in livestock.

The serious impact of RVF epidemics and epizootic is generally associated to a number of factors including:

- Morbidity and mortality in livestock
- Disruption into the meat industry resulting from the ban in livestock slaughter;
- Disruption to livestock markets
- Subsequent disruption to the livelihood of all actors in the livestock value chain
- Disruption to the country's economy, including tourism

As a matter of fact, RVF impacts heavily on pastoralists who keep and trade small and large ruminant. In the horn of Africa Export of livestock income, most of which come from pastoralists, can represent up to $300 million USD [20][6]

Socio-economic impact of RVF epizootics is well summarised in the Figure 8 below. Sadly, socio-economic impact studies have been so far conducted only on a limited number of countries, mainly in East African and the Horn of Africa regions (Kenya, Tanzania, Sudan, Somalia etc.) and in South Africa.

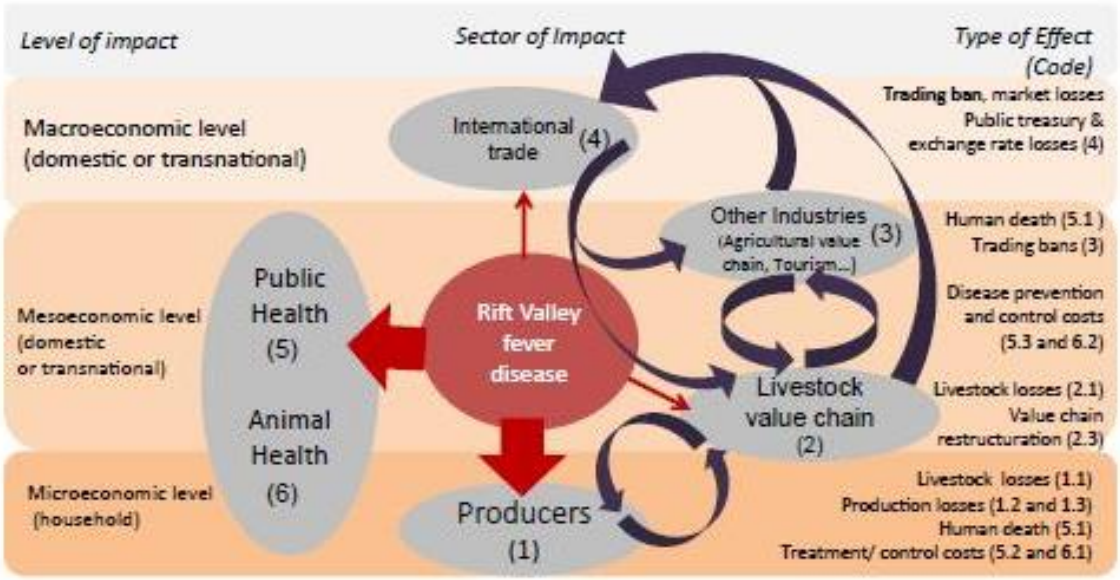

Figure 8: Socio-economic impacts of RVF per sector, level and type of effects induced. The links between the disease and the different sectors and level impacted (health related costs) are represented by straight (red) arrows; the links between the different sectors and level impacted (non-health related costs) are represented by the bent (blue) arrows. (Source: [43])

Table 9: Overview of the different types of socio-economic impact induced by Rift Valley fever, their broad characteristics and their estimation from field case studies. (Source: [43])

Impacted sector (code)	Level[a]	Category	Type of Effect (code) (timescale[b])	Financial estimate per country (Reference)
Producers (1)	Microeconomic Household economy	Food security and livelihood economy	Livestock losses (1.1) (short term)	Kenya: $9.3 million USD (Lichoti, 2009; Rich et al., 2009; Rich and Wanyoike, 2010; Sindato et al., 2012)
				Somalia: $47–55 million USD (Ahrens, 1998; Soumaré et al., 2006)
				Yemen: $0.6 million USD (Handlos, 2009)
				Saudi Arabia: no estimates
			Losses in production (1.2) (short term)	Kenya, Milk ($2 million USD) (Lichoti, 2009)
				Somalia, Yemen, Saudi Arabia: no estimates
			Abortion; destocking; redistribution effects (inequalities) (1.3) (long term)	No estimates
Livestock industry (2)	Mesoeconomic Domestic or	National economy Food security	Livestock losses (2.1)	Kenya ($32 million USD) (Rich et al., 2009; Rich and Wanyoike, 2010; Orinde et al., 2012)

	transnational	Livelihood economy	(short term)	Yemen ($15 million USD) (Handlos, 2009)
				Saudi Arabia ($5.3 million USD) (Mohammed, 2007)
				Somalia, no estimates
			Trading bans impact on local value chain (local market losses) (2.2) (short term)	Kenya ($10 million USD) (Rich and Wanyoike, 2010; Orinde et al., 2012 Somalia ($29–45 million USD) (Ahrens, 1998; Holleman, 2002; Nin Pratt et al, 2005; Cagnolati et al., 2006; Soumaré et al., 2006) Yemen, Saudi Arabia: no estimates
			Value chain restructuration, consumer perception (2.3) (long term)	No estimates
Other Agro-industries (3)	Mesoeconomic Domestic or transnational	National economy	Transport; tourism; trading bans (3) (short and long term)	Yemen, tourism ($30 million USD) (Handlos, 2009) Kenya, Somalia, Saudi Arabia: no estimates
International Trade (4)	Macroeconomic	National economy	Trading bans impact on import/export; public treasury and exchange rate losses (4) (short and long term)	Kenya ($ 10 million USD) (USAID, 2008; Rich and Wanyoike, 2010; Orinde et al., 2012; 44)
				Somalia ($330 million USD) (Ahrens, 1998; Holleman, 2002; Nin Pratt et al.,

				2005; Soumaré et al., 2006) Yemen ($50 million USD) (Handlos, 2009) Saudi Arabia: no estimates
Public health (5)	Microeconomic Household and Mesoeconomic Domestic	Livelihood & National economies	Human death (5.1) Private treatment (5.2) (short and long term)	Kenya 1% of total DALY (household costs: $82 000 USD) (Orinde et al., 2012) Yemen ($12 million USD, human death) (Handlos, 2009)
			Prevention and control (human infections) (5.3) (short and long term)	Somalia and Saudi Arabia: no estimates
Animal health (6)	Microeconomic household and Mesoeconomic Domestic	Livelihood and national economies	Private surveillance and control in livestock (6.1) (Short and long term) Public surveillance and control in livestock (6.2) (short and long term)	Kenya ($2.5 million USD, short term) (Lichoti, 2009; Rich & Wanyoike, 2010) Yemen ($ 0.1 million USD, vector control) (Handlos, 2009) Somalia, Saudi Arabia: no estimates

Table 10: Number of RVF outbreaks reported to the AU-IBAR from 2005 to 2015 (numbers given only for the target countries). Source: AU-IBAR Year Books.

Year	Country	Human		Animal		Estimated economic impact	
		Cases	Deaths	Cases	Deaths	US$ ($x10^6$)	%GDP (PPP)
1950–1951	South Africa	nd	nd	600 000	100 000	nd	nd
1977–1978	Egypt	200 000	594	nd	nd	115	0.8
1978	Zimbabwe	nd	Nd	70 000	10 000	nd	nd
1997–1998	East Africa[a]	89 000	478	nd[b]	Nd	>250	nd[c]
2000–2001	Saudi Arabia	883	123	>10 000	1000	10	0.02
2000–2001	Yemen	1328	166	22 000	6000	107	0.8
2006–2007	Kenya	684	155	>4400	235	66	0.1
2006–2007	Somalia	114	51	nd	Nd	471	5.5
2006–2007	Tanzania	264	109	32 000	4200	6,7	0.01
2008–2009	Madagascar	>650	21	23	18	nd	nd
2008	Sudan	698	222	nd	Nd	nd	nd
2010–2011	South Africa	186	18	>15 000	9000	nd	nd

This list is a non-exhaustive list, and complete information on RVF outbreaks could be found on World Animal Health Information database (WAHID) at **http://www.oie.int/wahis/public.php** $USD, United States Dollar; GDP (PPP), gross domestic product at purchasing power parity; nd, not determined. [a]Kenya, Somalia and Tanzania, [b]Only available for Kenya: 70% of sheep population, 20–30% of camel and cattle, [c]Available for Somalia: US$186 million, 4.3%GDP (PPP).

Disease Prevention and Control Methods

Theoretically tools that could be used for the control and prevention of RVF epizootics include vector control, surveillance and early warning systems, better herd immunity and treatment.

Early detection

Given the long and inconsistent inter-epidemic period in RVF enzootic regions and the devastating nature of outbreaks, it has become critical to put in place early detection and warning systems and mechanisms, especially in endemic and high-risk regions.

For early detection of the disease, a commonly used practice in Africa has been the use of Sentinel Animals. Sentinel herd monitoring has been used in different parts of Africa to monitor viral circulation in susceptible populations. It can be enhanced by the additional monitoring of climatic parameters.

- Sentinel animals are usually located or established in geographically representative areas, and in zones where mosquito breeding activity is likely to be greatest, e.g. near rivers, swamps and dams.
- In order to be effective and more reliable, sentinel herds should be monitored in conjunction with the monitoring of other risk indicators such as climatic parameters.
- Generally 30 naïve young female sheep or goats, 12 to 15 months old are selected after the owners have been sensitised and incentivised (such as free deworming etc.). It is recommended that not less than 20 animals are kept at each location
- They are screened for freedom of IgG and IgM in order to be included in the sentinel program. They should then be monitored regularly.

Unfortunately, many established sentinel herds in several African countries (Senegal, Mauritania, Kenya) are not regularly screened due to the high cost of commercial diagnostic tests (ELISA) and the cost involved in their regular monitoring, as they tend to be in areas remotely located from laboratories.

Early warning and satellite imagery

Each of the documented moderate or large RVF outbreaks that have occurred in the Horn of Africa over the last 60 years have been associated with El Niño/Southern Oscillation (ENSO) phenomena above normal and widespread rainfall, except for few localised cases [2].

Retrospective analysis of a satellite-derived time series vegetation measurements of photosynthetic activity, known as the normalized difference vegetation index [2], has shown that such data, in combination with other climate variables, can be used to map areas where RVF occurred.

Based on the above, satellite and other data have been allowing in recent years the FAO, through its Emergency Prevention System for Transboundary Animal and Plant Pests and Diseases (EMPRES)/Livestock Programme, to warn certain countries, at the most, 3 months in advance, of RVF risk.

Treatment

To date there is no effective chemotherapy or other form of treatment for livestock.

Prophylaxis (Prevention)

Vector control

The viability of mosquito eggs in dambo soil can be reduced by burning of the grass cover, and strategically-timed application of larvicides can be used to suppress mosquito breeding.

Other measures, such as chemical control of adult vectors, movement of stock from low-lying areas to well-drained and wind-swept pastures at higher altitudes, or confining of animals to mosquito-proof stables, are usually impractical, instituted too late and at best palliative in the face of a RVF epidemic.

Immunization

Immunization remains the only effective method of protecting livestock. It is however practices differently in different endemic countries (Table 11):

- Countries practicing or recommending preventive yearly vaccination, even during inter-epidemic period: South Africa and other Southern African countries (Namibia, Botswana), Saudi Arabia, Egypt
- Countries vaccinating on first indications of outbreaks: Kenya, Tanzania, Sudan

- Countries not practicing vaccination even during epidemics: Mauritania, Madagascar, Senegal

Until the recent registration of RVF Clone 13 in South Africa in 2009, the only available RVF vaccines were the live attenuated Smithburn, produced by OBP and KEVEVAPI in South Africa and Kenya respectively, and the inactivated vaccine produced in limited quantities by OBP and the Egyptian Vaccine and serum institute. The poor safety of the Smithburn, especially in pregnant animals and the need for a booster dose after primo-vaccination for the inactivated RVF had prevented many countries in Africa, especially in West Africa, to institute vaccination. This has resulted in lack of effective control during outbreaks or in inter-epidemic periods.

The RVF Clone 13 although safer than the Smithburn vaccine and requiring single vaccination (advantage over the inactivated vaccine) is still not widely available and currently has been discontinued by OBP due to stability problems.

Table 11: Control strategies for RVF depending on its epidemiological situation

RVF Situation	Examples of countries	Current control strategy
Endemic with regular outbreaks	Kenya, Tanzania, Egypt, Senegal, Mauritania	• Vaccination at first sign of an outbreak: Kenya, Tanzania. • Continuous vaccination: Egypt • No vaccination: Mauritania, Senegal
Endemic with sporadic / re-occurring outbreaks	South Africa, Saudi Arabia	Continuously / yearly vaccination
Free – High risk	Middle East, North Africa	(Active) surveillance
Free – Low risk	Europe, Americas	Surveillance, talks of vaccine banks.

Disease situation and government policies by country

Tables 12 and 13 will be updated and completed once the results from the questionnaires sent to the DVS offices of the different countries are received.

The first table covers the disease situation (if it is notifiable or not), the presence of official surveillance and/or control programs, and the treatment situation. The second table refers to vaccination.

The definitions that were given to the respondents are:

[1]Surveillance: is the systematic ongoing collection, collation and analysis of data and the timely dissemination of information to those who need to know so that action can be taken.

[2]Control: a programme which is approved, and managed or supervised by the Veterinary Authority of a country for the purpose of controlling a vector, pathogen or disease by specific measures applied throughout that country, or within a zone or compartment of that country

Table 12: Official status, official programs for RVF in the countries of interest

Country	Notifiable (yes/no)	Official surveillance[1] program (yes/no) If yes, active or passive	Official control[2] program (yes/no)	Treatment (Chemotherapy)	
				Treatment authorised (yes/no)	Frequently practiced (yes/no)
Burkina Faso					
Côte d'Ivoire (Ivory Coast)	Yes	-	No	-	-
Ethiopia					
Kenya	Yes	Yes, active & passive	YEs	No	No
Madagascar					
Malawi	Yes	Yes, passive	No	N/A	N/A
Mali	Yes	Yes, passive	N/A	N/A	N/A
Mozambique					
Rwanda	Yes	Yes, active & passive	Yes	Yes	No
Senegal					
South Africa					

Tanzania	Yes	Yes, active & passive	Yes	No	No
Uganda	Yes	No	No	N/A	N/A
Zambia	Yes	Yes, passive	Yes	N/A	N/A

-: Questionnaire left blank by respondent

Table 13: Vaccination for RVF in the countries of interest

Country	Vaccination			
	Compulsory vaccination (yes/no)	Who pays for the vaccine (Government, farmers, combination, others-specify)	Who delivers the vaccine (official, private vaccinators or both)	Species vaccinated (cattle, sheep, goats, pigs, poultry)
Burkina Faso				
Côte d'Ivoire (Ivory Coast)	No	-	-	-
Ethiopia				
Kenya	As per control program	Combination	Both	Cattle, sheep and goats
Madagascar				
Malawi	No	N/A	N/A	N/A
Mali	N/A	N/A	N/A	N/A
Mozambique				
Rwanda	Yes	Government	Official	Cattle, goats and sheep
Senegal				

South Africa				
Tanzania	Yes	Government, Private, NGO	Both	Cattle, sheep, goats
Uganda	No	Never vaccinated	N/A	N/A
Zambia	No	N/A	N/A	N/A

-: Questionnaire left blank by respondent

Additional vaccine and vaccination strategies for RVF control

One of the biggest challenges to the control of RVF through the use of vaccines remains the design of suitable vaccination strategies. The cyclical nature of the disease and the subsequent long inter-epidemic periods have resulted in many countries considering the use of vaccination only at first indication of an outbreak.

Control strategies that promote the establishment of good herd immunity in the livestock population in endemic regions are more likely to reduce the devastating impact of severe outbreaks. As discussed earlier, a number of factors prevent many endemic countries from putting into place effective control strategies for RVF. Key obstacles to effective RVF control include:

- The cyclical nature of RVF and long inter-epidemic period;
- The specific policies on the control of RVF or lack of emergency preparedness strategy for RVF outbreaks in many countries;
- Poor diagnostic capacity when the diagnostic laboratory is located far from high risk areas where the disease tends to start, while limited resources prevent the conduct of RVF activities outside outbreak seasons (high cost of diagnostic tests, logistical challenges in regular transport of samples from sentinel animals etc.); and
- The high pressure on the few RVF vaccine manufacturers, because of their limited production capabilities, when there are outbreaks in more than one country.

In order to address these two initiatives have been explored: the use of combination vaccinations and vaccine banks or strategic reserves.

1- Combination vaccines including RVF and a vaccine for a disease widely and regularly use, such as Sheep & goat pox for small ruminants, and Lumpyskin for cattle have been explored for a number of years now. The idea is that such vaccines would rely on the regular vaccination of animals for Lumpyskin disease in cattle and sheep and goat pox in sheep and goat respectively, in order to build immunity in vaccinated animals to RVF. Pox

recombinant vaccines with Lumpyskin or sheep/goat pox as vector have been tried by different groups with little progress toward a commercial vaccine to date. A combination vaccine including RVF Clone 13 and Lumpyskin Neethling strain was evaluated by OBP, but with limited progress to date due to the poor stability of the OBP Clone 13 vaccine.

2- A RVF vaccine/vaccine antigen bank for a monovalent RVF vaccine: the concept is to use strategic stocks of vaccine managed by the manufacturer for a region, or vaccine antigens stocked taking into account the need for emergency production.

Vaccine banks or strategic stocks are suitable for Regional strategies for the control of RVF, and are expected to encourage more cohesive policies and mutual support between different countries. A number of initiatives were initiated in the Southern Africa Development Community (SADC) region. These initiatives included the evaluation of RVF risk in each country through the development of risk maps based on historic data on the occurrence of the disease, a RVF policy landscaping in order to understand current policies setup in each country around RVF control, and the establishment of a technical RVF [11]

An additional tool that is required for a more effective RVF vaccination strategy is a RVF field test in the form of lateral flow device or pen-side test, which allows for testing animals in situ, avoiding costly shipment of serum specimens to laboratories.

Vaccines Available

There are different types of vaccines for RVF. Table 14 shows a summary of the characteristics of the main vaccines and its commercial status.

Table 14: Vaccination for RVF in the countries of interest

Vaccine	Strain	Status
Inactivated (OBP, VSVRI)	Pathogenic field strain	Commercially available since 1970s in SA. Essentially used in cattle.
Live attenuated (OBP, KEVEVAPI)	Smithburn	Commercially available
Avirulent natural mutant	Clone 13: natural deletion in S segment	Registered in SA. Production suspended due to stability challenges

Commercial vaccines manufactured in Africa and Asia

The information summarised in Table 15 is based on information from The Center for Food Security and Public health, Iowa State University (**www.cfsph.iastate.edu/vaccines/index.php** and Vetvac (**www.vetvac.org**). More details have not been gathered, as it has been assigned to another consultant.

To date registered commercial RVF vaccines are only produced in South Africa, Kenya and Egypt. MCI in Morocco has also registered a RVF Clone 13 vaccine which has not yet been used in another country. African countries other than the above three that have used the RVF vaccine are Namibia, Botswana, Tanzania, and Sudan. They have generally imported the RVF vaccine from OBP in South Africa and to a limited extent from KEVEVAPI.

Table 15: RVF vaccines manufactured in Africa

Manufacturer	Country	Name & Strain	Vaccine Type	Countries distribution
Onderstepoort Biological Products	South Africa	Smithburn	Live	South Africa, Namibia
		RVF inactivated vaccine	Killed	South Africa
		RVF Clone 13	Live	South Africa
Veterinary Serum and Vaccine Research Institute	Egypt	Smithburn	Live	Egypt
		RVF inactivated vaccine Zagazig H501	Killed	Egypt, Arab Rep.
KEVEVAPI	Kenya	Riftvax Smithburn	Live	Kenya
MCI Santé Animale	Morocco	Clone 13T	Live	Morocco

Commercial vaccines imported into Africa

The information summarised in Table 16, is based on a questionnaire send to the Director of Veterinary Services office and regulators of the countries of interest. Note that some vaccines might have been imported under DVS dispensation, and they are not necessary licensed in the country.

Table 16: RVF vaccine imported into the different countries

Country	Vaccine name	Strain or type	Country of origin	Doses imported 2015	Doses imported 2014	Doses imported 2013	Doses imported 2012
Burkina Faso	N/V**						
Côte d'Ivoire (Ivory Coast)	N/V						

Ethiopia	N/V						
Kenya	-	-	-	-	-	-	-
Madagascar							
Malawi	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mali	N/V						
Mozambique							
Rwanda	Riftvax		Kenya	55,000	40,000	25,000	5,000
Senegal	N/V						
South Africa							
Tanzania	Smithburn		South Africa				400,000
Uganda*	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Zambia		Smithburn	South Africa			1,500	
		Clone 13	South Africa			2,000	
		Live attenuated	South Africa		23,300	10,000	
		N/A	South Africa	11,000		35,600	
		Inactivated	South Africa	75,000			

* Source: Head of the local regulatory agencies; **N/V: Never vaccinated

Characteristics of Ideal Vaccine Candidates for Smallholders

Preventing and controlling RVF through vaccination will be based on different key principles whether it is for an endemic region or for a region at risk of new introduction. In other word, while there are generic characteristics that the vaccine should have, some will be specific to endemic regions and other for regions free of the disease, and at risk.

As is the case for many diseases endemic in certain areas and posing a risk to free countries, the key characteristics of the ideal vaccine may vary. Below are some attributes that will be needed for vaccines targeting endemic and free at-risk countries

- ***Generic characteristics***
  - **Safety**
    - Safe to produce
    - Safe to all physiological stages of animals
    - No residual virulence
    - No risk of introduction into the environment (shedding, persistence in animals etc.)
    - No risk of spread to human or other species
  - **Efficacy**
    - Protection of all susceptible species
    - Quick onset of protective immunity, including in young animals
    - Long lasting immunity
    - STOP TRANSMISSION: prevent amplification of RVFV in ruminants
  - **Vaccination**
    - Cost effective for producers and users
    - Single vaccination
    - Ease of application
    - Suitable for stockpiling (vaccine or antigen bank) and quick availability
- ***Endemic regions***
  - Continuous vaccination: yearly vaccination of susceptible livestock
    - Need to know how many vaccinations may be required to build a life long immunity
  - **Efficacy**
    - Solid protective immunity after 1 vaccination
- ***Free regions***
    - Quick onset of protective immunity
    - Protective in young animals and possibly newborn naïve animals
    - Sterilizing immunity
    - DIVA

Some of the major characteristics to be considered for the ideal RVF vaccine were summarised at GF-TADs meeting organised by the FAO in January 2011:

Safety

No reversion to virulence;
Lack of abortion in vaccinated animals; and
Non-teratogenic

Efficacy

Prevention of viremia;
Rapid onset of immunity;
Long-lasting immunity;
Prevention of abortion on challenge;
Prevention of clinical disease;
Produce immunity in young animals;
Target key susceptible ruminant species; and
Single-dose regimen

The Target Product Profiles (TPPs) reflect the availability and utility of current agents and incorporate features that will be necessary to improve on the current products and to address unmet needs, taking into account the particular requirements of the poorest livestock keepers.

The TPPs are more robust when they include the opinions and consider the needs of the different stakeholders. While efforts have been made to encompass them, the TPP in Table 17 below should be considered a proposal, a live document subject to improvements.

Table 17: Target Product Profile (TPP) RVF vaccine

	Attribute	Minimum (current available vaccine)	Ideal
1	Antigen	Immunogen with protective antigens of RVFV	Immunogen with protective antigen of RVFV
2	Indication for use	For active immunization of sheep, goats & cattle	For active immunization of sheep, goats, cattle and camels
3	Recommended species	Cattle, Sheep and goats	All RVF susceptible livestock

4	Recommended dose	2 ml	1 ml
5	Pharmaceutical form	Reconstituted injectable solution/suspension (freeze-dried vaccine) or ready to use solution (inactivated vaccine)	Ready to use solution/suspension
6	Route of administration	SC	SC, Intramuscular or pour on
7	Regimen - primary vaccination	Single dose	Single lifetime dose
8	Regimen - booster	Single annual booster	Lifelong immunity after primary vaccination
9	Epidemiological releance	Protection against *RVF*	Protection against RVF and prevention of virus transmission
10	Recommended age at first vaccination	• Animals over 6 months: one injection • Animals under 6 months: two injections at a 2 to 6 month interval; the second injection should only be given to animals over 6 months old.	From 1-2 months of age
11	Onset of immunity	2-3 weeks following primary vaccination	One week following primary vaccination
12	Duration of immunity	At least 1 year	Lifelong immunity
13	Expected efficacy	To prevent disease & prevent mortality.	To prevent infection and transmission. No disease & no mortality in vaccinated animals after virulent challenge.
14	Expected safety	In animals under 6 months of age, a transient pyrexia reaction can occur. A transient nodular reaction of varying importance, may appear at the injection site, it progressively disappears within 1 to 2 months. Only	No post-vaccinal reactions at any age. Safe for pregnant animals.

		vaccinate pregnant animals on emergency.	
15	Withdrawal period	Nil	Nil
16	Special requirements for animals	Do not vaccinate un-healthy animals	Do not vaccinate un-healthy animals DIVA
17	Special requirements for persons	None	None
18	Package size	50 doses	Multiple pack size from 20 doses
19	Price to end user	Not more than $0.50/dose	$0.20/dose at end user
20	Storage condition and shelf-life as packaged for sale	12 months at 4-8° C	24 months 4-8° C and/or 48 hours at 30° C
21	In-use stability	1 hour	24 hours

Overall conclusion for improved RVF control through vaccination

Some important point for consideration, that would lead to the ideal vaccine are discussed below

Need for validated challenge models not posing a risk to the researchers:

The most suitable way to evaluate a RVF vaccine is through challenge studies, involving a virulent RVFV strain. There are also a limited number of virulent RVFV strains around, that are capable of consistently reproducing the disease. In vitro models could be considered but most of them are not properly validated. There is therefore a need for reliable fully validated challenge models in target animals; while also validated correlate for protective immunity for in vitro efficacy models.

Promote the development of multivalent vaccines including RVF:

This will indirectly improve the uptake of RVF vaccine through continuous vaccination, thus improve herd immunity to RVF. Likely combination include LSD-RVF; using a LSD strain that is also protective against sheep and goat pox would make such vaccine suitable for both cattle, sheep and goat, all over affected regions of Africa. Another combination is RVF with CBPP, for use in cattle in East and Western Africa.

Promote RVF vaccine bank (stockpile or strategic reserves) at regional levels

Considering the fact that RVF epidemics generally affect several countries simultaneously, putting a strain on vaccine production capacity, preparedness strategies should include strategic reserves or antigen, half product or ready to use vaccines. The size of the reserve should be determined on the basis of risk mapping studies in affected countries.

Additional considerations indirectly connected to the above are:

- The need for an effective human vaccine (to protect livestock keepers, but also research and animal health personnel)
- The need for field diagnostic assay
- Development of risk maps in all endemic countries, similar to those already produced for Kenya and South Africa

The present review has discussed a large number of candidate RVF vaccines developed to date, and having reached different stages of development. There is still no candidate that has demonstrated DIVA characteristics, although theoretically this seems to be possible with some of them. There is also a need to demonstrate the ability of these candidates to meet the TPP and key characteristics discussed earlier, such as the ability to prevent transmission and viremia, early onset of immunity, long lasting immunity after single dose, prevention of abortion on challenge etc.

An area that still needs much more work and focus is the development and implementation of appropriate vaccination strategies, or control strategies involving vaccines. Given the fact that the bulk of endemic countries do not vaccinate during inter-epidemic periods - and some not even around declared epidemics - calls for more solid strategies around vaccination. This should include regional approaches relying on tools such as vaccine banks, multi-vaccines, field tools for active surveillance (sentinel animals and field diagnostic assays etc.). There are opportunities to pilot such programs at regional level in Africa, building on lessons learned to date.

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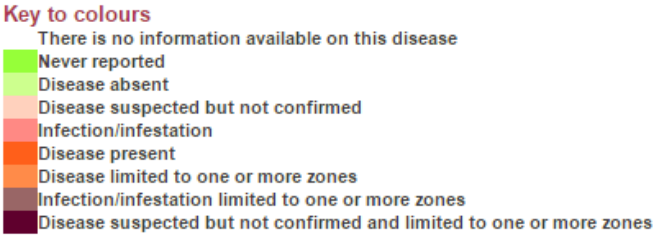
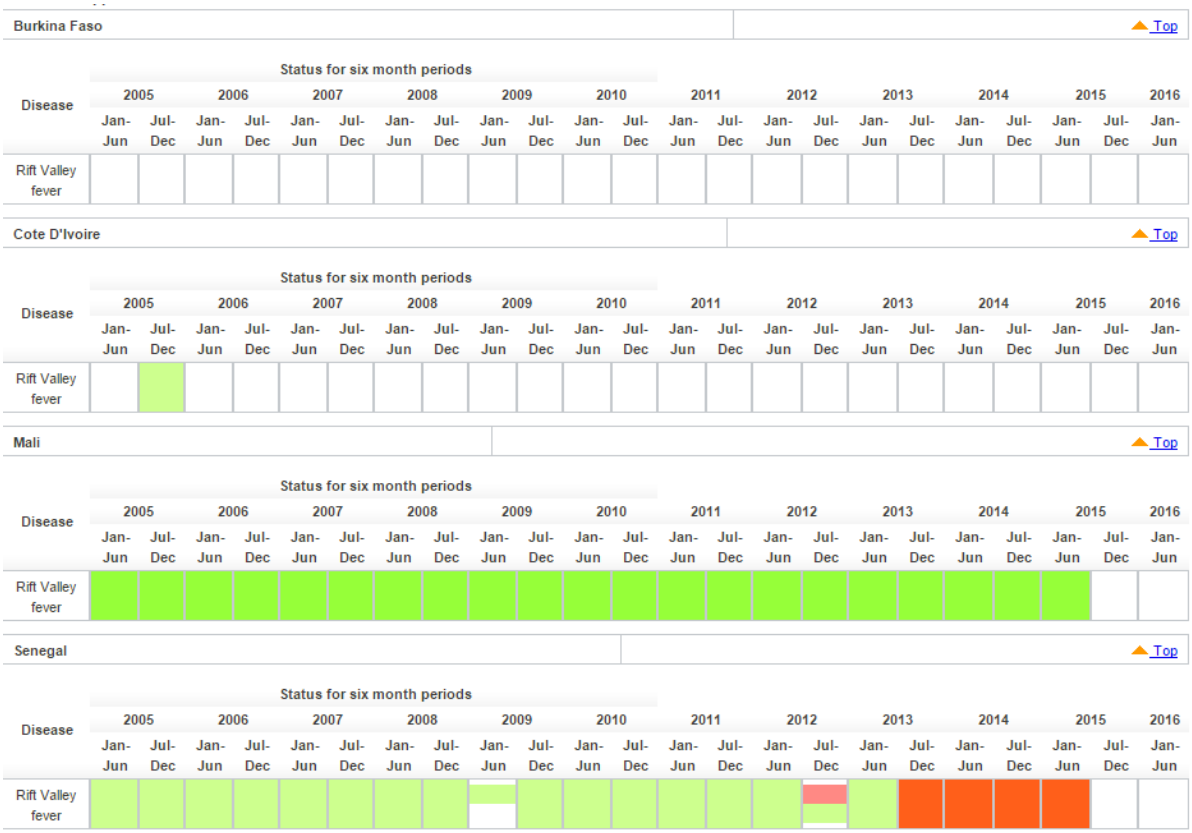
ANNEX 1: Additional data on disease presence and incidence

Reports to OIE on RVF:

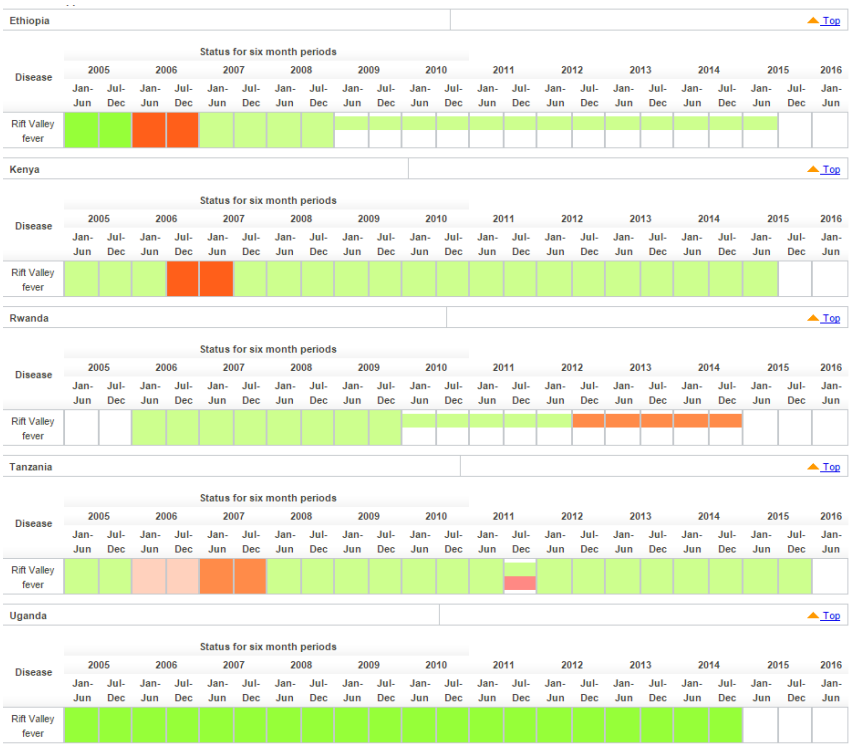


When different animal health statuses between domestic and wild animal population are provided, the box is split in two: the upper part for domestic animals, and the lower part for wild animals.

RVF in Western Africa: Burkina Faso, Ivory Coast, Mali and Senegal



RVF in Eastern Africa: Ethiopia, Kenya, Rwanda, Tanzania and Uganda



RVF in Southern Africa: Madagascar, Malawi, Mozambique, South Africa and Zambia